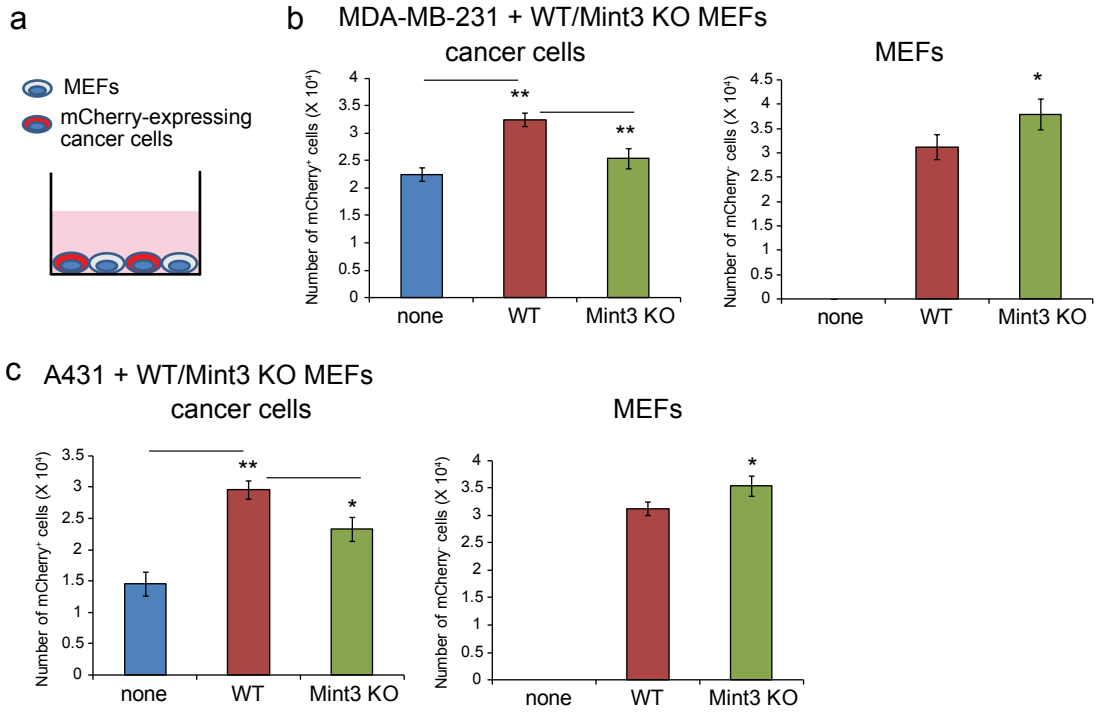
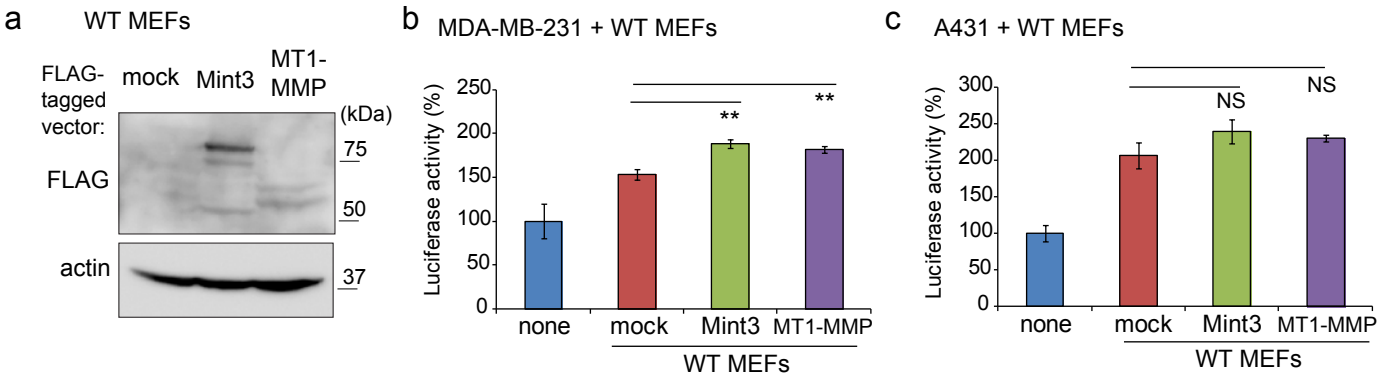


Supplementary Figure 1. Mint3 KO MEFs defect in promoting cancer cell proliferation.

(**a**) Illustration of co-culture experiments.

(**b**, **c**) mCherry-expressing MDA-MB-231 (b) and A431 cells (c) were co-cultured with MEFs for 48 h, and mCherry-positive cancer cells (left panel) and mCherry-negative MEFs (right panel) were counted.

In **b** and **c**, error bars indicate the s.d. (n = 3). The data were analysed using a t test. *p < 0.05, **p < 0.01. The data shown in **b-d** are representative of 3 independent experiments with similar results.



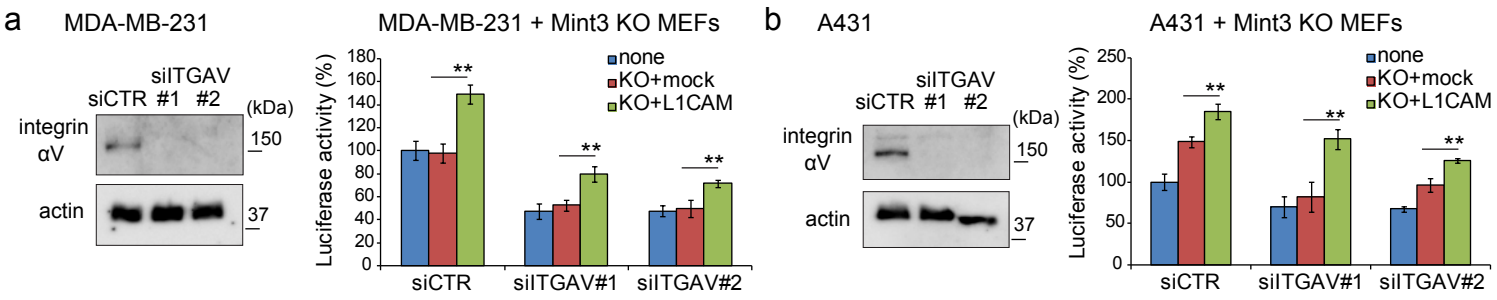
Supplementary Figure 2. Exogenous expression of Mint3 and MT1-MMP in WT MEFs slightly promotes proliferation of MDA-MB-231 cells.

(**a**) Western blot analysis of mock, FLAG-tagged Mint3, and FLAG-tagged MT1-MMP expression in WT MEFs.

(**b**, **c**) Secreted luciferase activity from GLuc-expressing MDA-MB-231 (**b**) and A431 cells (**c**) co-cultured with mock, Mint3, or MT1-MMP expressing WT MEFs.

In **b** and **c**, error bars indicate the s.d. (n = 3). The data were analysed using a t test. **$p < 0.01$. NS, not significant.

The data shown in **a-c** are representative of 3 independent experiments with similar results.

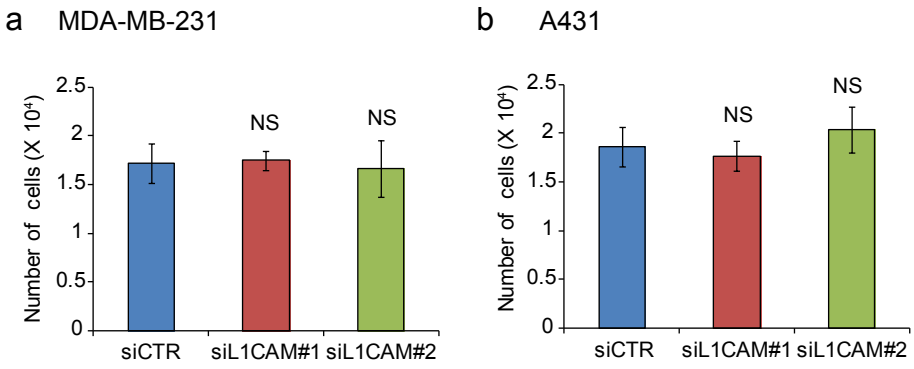


Supplementary Figure 3. Knockdown of Integrin αV in cancer cells does not affect MEF-mediated proliferation of MDA-MB-231 and A431 cells.

(**a**, **b**) (left panel) Western blot analysis of integrin expression in MDA-MB-231 (**a**) and A431 cells (**b**) treated with control (CTR) or integrin αV (ITGAV) siRNA. (right panel) Secreted luciferase activity from siRNA-transfected GLuc-expressing MDA-MB-231 (**a**) and A431 cells (**b**) co-cultured with mock or L1CAM expressing Mint3 KO MEFs.

In **a** and **b**, error bars indicate the s.d. (n = 3). The data were analysed using a t test. **p < 0.01. NS, not significant.

The data are representative of 3 independent experiments with similar results.

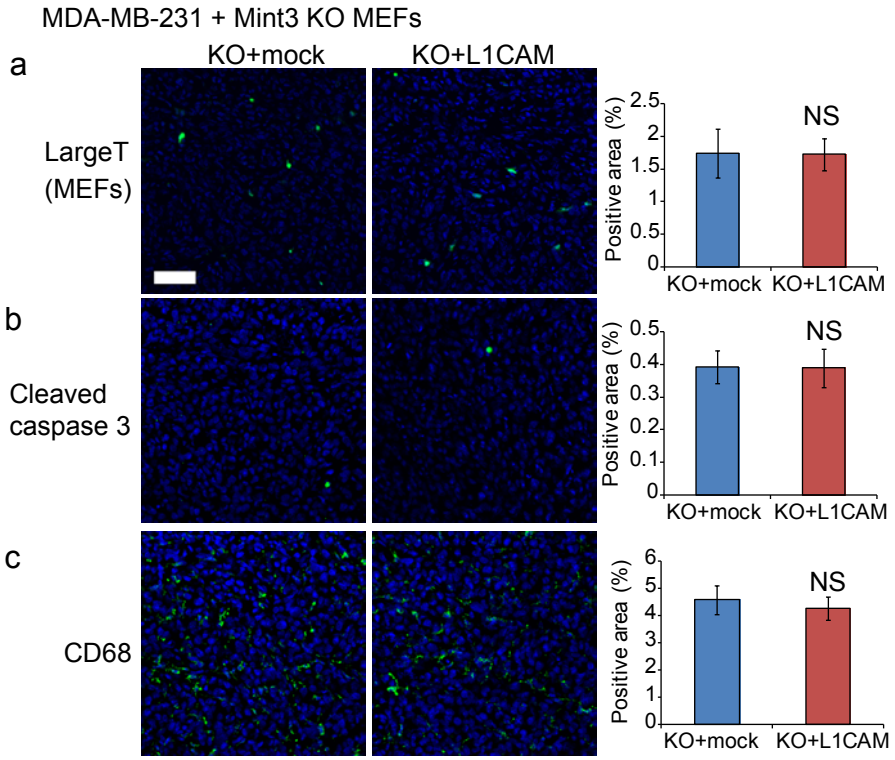


Supplementary Figure 4. Knockdown of L1CAM does not affect proliferation of MDA-MB-231 and A431 cells.

(**a**, **b**) Cell number of GLuc-expressing MDA-MB-231 (**a**), A431 cells (**b**) transfected with control (CTR) or L1CAM siRNA.

In **a** and **b**, error bars indicate the s.d. (n = 3). The data were analysed using a t test. NS, not significant.

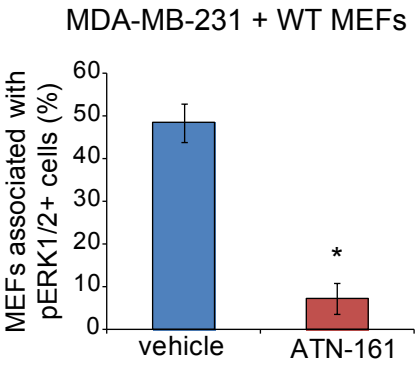
The data are representative of 3 independent experiments with similar results.



Supplementary Figure 5. L1CAM expression in Mint3 KO MEFs does not affect the number of MEFs, apoptotic cells, and macrophages in tumour tissues of MDA-MB-231 cells co-cultured with MEFs.

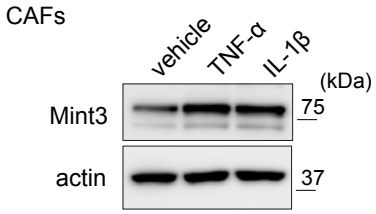
(**a-c**) Immunostaining of SV40 large T antigen (**a**), cleaved caspase 3 (**b**), and CD68 (c) in tumour tissues of MDA-MB-231 cells cultured with mock or L1CAM expressing Mint3 KO MEFs at day 10 (left panel). Bar = 50 μm. Positive areas for each staining were analysed (right panel).

In **a-c**, the error bars indicate the s.e.m.; n = 9 from 3 tumours (3 fields/tumour); the data shown were analysed by using the Mann–Whitney U-test. NS, not significant.



Supplementary Figure 6. ATN-161 injection decreases the number of MEFs associated with phospho-ERK1/2 positive cells in tumour tissues of MDA-MB-231.

MDA-MB-231 cells were subcutaneously injected with WT MEFs into immunodeficient mice. At day 10 after tumour injection, mice were administered with vehicle or ATN-161 (2 mg/kg body weight) intraperitoneally, and tumour tissues were collected 4 h after injection followed by immunostaining analysis. The ratio of MEFs associated with phospho-ERK1/2 positive cells in tumour tissues was analysed. The error bars indicate the s.d.; n = 5 from 5 tumours (average of 5 fields/tumour); the data shown were analysed by using the Mann–Whitney U-test. *$p < 0.05$.

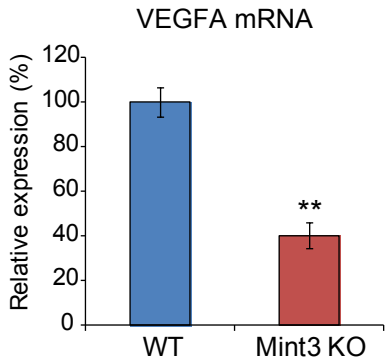


Supplementary Figure 7. Inflammatory cytokines increase Mint3 expression in CAFs.

CAFs were treated with vehicle, TNF-α (10 ng/mL), or IL-1β (10 ng/mL) for 24 h followed by western blot analysis.

The data are representative of 3 independent experiments with similar results.

MEFs



Supplementary Figure 8. Mint3 depletion decreased VEGFA expression in MEFs.

RT-qPCR analysis of VEGFA mRNA in WT and Mint3 KO MEFs. Error bars indicate the s.d. (n = 3).

The data were analysed by a t test. **$p < 0.05$. The data are representative of 3 independent experiments with similar results.

>2-fold genes (155)	
3830403N18Rik	Maf
4930432K21Rik	Mgat3
4930478M13Rik	Mtss1
6430553K19Rik	Neto2
6530409C15Rik	Ngef
6820445E23Rik	Notch3
AA408650	Npcd
Acot1	Nr1h3
Actn2	Oas1a
Adm2	Oas1f
Adssl1	Ogdhl
Afp	Olfm1
Amz1	Olfr1431
Anxa8	Ophn1
Aqp1	Parp10
Arap3	Pcdh12
Arhgap9	Pdcd1lg2
Artn	Pde2a
Asphd2	Pdgfb
B4galnt1	Pdgfra
Bace2	Pik3c2g
BC061237	Pip5kl1
BC068157	Pkp1
C130030K03Rik	Plek2
C1ql1	Plekho2
Cadm3	Ptges
Ccl17	Ptk2b
Cd276	Ptpn18
Cdc42ep5	Ptpn5
Cdsn	Ptpre
Cdyl2	Qpct
Ces1a	Reep1
Ces1g	Rgs17
Chrna4	Rhox3a
Cpa2	Rhox5
Crabp1	Rnf130
Crip1	Rnf183
Ctf1	Rnls
Cx3cl1	Sardh
Cym	Scara3
D930026N18Rik	Serpina10
Dlx4	Serpinb9f
Dnah7a	Sftpd
Dnajc22	Sgcd
Dusp2	Sh2d1b1
Elavl2	Slc16a3
Enpp2	Slc35g2
Fam129a	Slc7a2
Fam19a5	Slit3
Fat4	Slx
Foxred2	Smpdl3b
Gfpt2	Sp110
Gm10487	Spn
Gm10639	Srgap3
Gm12349	Stac2
Gm14625	Synpo
Gm14625	Sytl2
Gm15085	Tcf7
Gm1993	Tmem119
Gm2030	Trib2
Gm3776	Trim44
Gm4297	Trim46
Gm5072	Ucma
Gm5168	Ugt1a6b
Gm9889	Ulbp1
Grem1	Ulbp1
Gsc	Vmn1r124
Hapln4	Vmn1r132
Hmx2	Vmn2r96
Htr7	Vps13c
Igfbp6	Xdh
Igsf10	Xlr
Irx3	Zcwpw1
Lama5	Zfp296
Lef1	Zswim5
Lmcd1	
LOC552912	
Lrg1	
Luzp4	
Maats1	

<0.5-fold genes (191)		
1700017I07Rik	Gng13	Slc24a4
3830406C13Rik	Gpr126	Slc26a10
3830406C13Rik	Grhl1	Slc35f2
4930402H24Rik	Gspt2	Slc38a4
4930573O21Rik	Hal	Slc6a15
5830416P10Rik	Hoxa1	Snap91
9430014F16Rik	Hspa1a	Snca
9630025H16Rik	Igsf5	Speer4b
A930028N01Rik	Il3ra	Spint1
Abcb9	Irak3	St3gal6
Ablim1	Jakmip2	Stxbp5l
Acap1	Kcnf1	Stxbp6
Adam19	Kcnf1	Syce2
Adamtsl3	Klhl13	Tbx20
Adcy3	Klhl32	Tex19.1
Ahrr	Klk1b5	Tll1
Akip1	Krt75	Tmem141
Aldh1a1	Krtap1-4	Tmem246
Aldh1a7	L1cam	Trim71
Aldh1b1	Lca5l	Tspan13
Arhgap36	Lce1i	Tspan7
As3mt	Lct	Tspyl5
Asgr1	Ldb2	Ttbk1
Atf7ip2	Lin7a	Ubash3a
Atp2b2	Lmo1	Ubqlnl
Atp6v0a4	LOC101055644	Vat1l
Avpr1a	LOC101056168	Wdr78
AY074887	Lonrf3	Xk
B4galt4	Lphn2	Zfp169
Bex1	Lpl	Zfp518a
C530008M17Rik	Lrp2	Zfp65
Cd33	Lypd4	
Cd6	Lypd6	
Cdh13	Macrod2	
Cdkn1c	Mageh1	
Chd7	Map2	
Chst10	March1	
Cnn1	Mark1	
Cnrip1	Mid1	
Coch	Mpzl2	
Col2a1	Msl3l2	
Creld1	Msrb2	
Cspg4	Myo5b	
Cst7	Naa11	
Cth	Ndn	
Cyp2ab1	Nefm	
Dach1	Olfr173	
Dcn	Olfr677	
Dlk1	Olfr868	
Dync1i1	Olfr969	
Dysf	Parm1	
E2f6	Pcdh17	
Eda	Pdgfd	
Egln3	Pdlim3	
Eif4g3	Penk	
Elmod1	Perp	
Eml2	Pla2g2d	
Epas1	Plac8	
Epha1	Plac9a	
Erdr1	Plagl1	
Etv3l	Plxdc2	
Fabp12	Polr1b	
Fam115c	Pomc	
Fam131a	Postn	
Fam73a	Prl8a9	
Fam81b	Ptprb	
Fbxl7	Ptprz1	
Fgf14	Rab38	
Fign	Rbp4	
Frrs1l	Renbp	
Gabra2	Ret	
Gabra3	Robo1	
Galnt3	Rragb	
Gas6	Rundc3b	
Ggn	Scml2	
Glipr1	Sema6d	
Gm10276	Sfrp2	
Gm2795	Sgsm1	
Gm6093	Shroom2	
Gnai1	Slc16a7	

Supplementary Table 1. Lists of genes with >2-fold and <0.5-fold expression in Mint3 KO MEFs

Primer sequences

Actb (β-actin)	sense	5′-agatcaagatcattgctcctcct-3′
	antisense	5′-acgcagctcagtaacagtcc-3′
Hif1a	sense	5′-catttctcagtcgacacagc-3′
	antisense	5′-tgtcctgtggtgacttgtcc-3′
L1cam	sense	5′-caccctgaggcattacacct-3′
	antisense	5′-tgccagtgcagtagcagact-3′
Aqp1	sense	5′-gctgtcatgtacatcatcgcccag-3′
	antisense	5′-aggtcattgcggccaagtgaat-3′
Cx3cl1	sense	5′-gccattgtcctggagacgac-3′
	antisense	5′-ccaaggtgatcccaggtgtc-3′
Notch3	sense	5′-ttctcctgtcgttgtctccg-3′
	antisense	5′-ggcactcatctatgtcactttgg-3′
Pdgfb	sense	5′-gactccgtagatgaagatgg-3′
	antisense	5′-ttgcactcggcgattacagc-3′
Slc16a3	sense	5′-tcacgggtttctcctacgc-3′
	antisense	5′-gccaaagcggttcacacac-3′
Lpl	sense	5′-ccaatggaggcactttccag-3′
	antisense	5′-ccacgtctccgagtcctctc-3′
Ptprb	sense	5′-tctgcagacagaaagctagc-3′
	antisense	5′-tagaaggtagttggagtctg-3′
Vegfa	sense	5′-agagcagaagtcccatgaag-3′
	antisense	5′-ctggtagacatccatgaacttg-3′

shRNA sequences

shLacZ	5′-gcuacacaaaucagcgauuucgaaaaaucgcugauuuguguag-3′
shMint3#1	5′-gaugauggcgguggugacgggacgaaucccgucaccaccgccauca-3′
shMint3#2	5′-gcgguucuugguccuguaugacgaaucauacaggaccaagaaccgc-3′
shL1CAM#1	5′-gcugcuuugccagcaauaagccgaagcuuauugcuggcaaagcagc-3′
shL1CAM#2	5′-ggaugaacagcaagaucuugccgaagcaagaucuugcuguucaucc-3′

siRNA sequences

control siRNA	5′-gaucuacuggucugccuaa-3′
mouse HIF-1α (#1)	5′-caagcaacugucauauaua-3′
mouse HIF-1α (#2)	5′-cuuugauguggauagcgau-3′
mouse FIH-1 (#1)	5′-ccauaaguucuuauacuau-3′
mouse FIH-1 (#2)	5′-guauugcacgcugcacuua-3′
mouse L1CAM (#1)	5′-caaugacacuggacgcuau-3′
mouse L1CAM (#2)	5′-caguaguucugccuugcaa-3′
human integrin β1 (#1)	5′-cuguucuuuggauacuagu-3′
human integrin β1 (#2)	5′-cuuacucaaugaaagacga-3′
human integrin α5 (#1)	5′-cagauaacuucacccgaau-3′
human integrin α5 (#2)	5′-cacuuuccaugcccagaau-3′
human integrin αV (#1)	5′-cuuuacugcugauagugcu-3′
human integrin αV (#2)	5′-cacauugguuaccacuaau-3′
human MT1-MMP (#1)	5′-gguucuggcgggugaggaa-3′
human MT1-MMP (#2)	5′-gauggauacccaaugccca-3′
human L1CAM (#1)	5′-cacacaaccugaccgaucu-3′
human L1CAM (#2)	5′-ccaagauccugacugcgga-3′

Antibodies (Western blot)

antibody	dilution
anti-V5 mouse antibody (R960-25; Thermo Fisher Scientific)	1:1000
anti-actin mouse antibody (MAB1501; Merck Millipore)	1:1000
anti-Erk1/2 rabbit antibody (#4695; Cell Signaling Technology,)	1:1000
anti-phospho-Erk1/2 (Thr202/Tyr204) rabbit antibody (#4370; Cell Signaling Technology)	1:1000
anti-integrin α5 mouse antibody (51-9001996; BD Biosciences)	1:1000
anti-integrin αV rabbit antibody (ab124968; Abcam)	1:500
anti-integrin β1 mouse antibody (51-9001995; BD Biosciences)	1:1000
anti-Mint3 mouse antibody (611380; BD Biosciences)	1:1000
anti-MT1-MMP mouse antibody (MAB3328; Merck Millipore)	1:1000
anti-laminA/C mouse antibody (612162; BD Biosciences)	1:1000
anti-HIF-1α mouse antibody (H1alpha67; Abcam)	1:1000
Anti-FLAG rabbit antibody (F7425; Sigma)	1:1000
anti-L1CAM goat antibody (SC-1508; Santa Cruz Biotechnology)	1:250
anti-FIH-1 goat antibody (SC-26219; Santa Cruz Biotechnology)	1:250

Antibodies (immunostaining, cell)

Antibody	dilution
anti-V5 mouse antibody (R960-25; Thermo Fisher Scientific)	1:500
anti-mouse IgG conjugated to Alexa Fluor 488 goat antibody (A-11029; Thermo Fisher Scientific)	1: 2000

Antibodies (immunostaining, frozen section)

Antibody	dilution
rabbit anti-cleaved caspase-3 antibody (#9579; Cell Signaling Technology)	1:100
rabbit anti-Ki67 antibody (RM-9106-S0; Thermo Fisher Scientific)	1:400
mouse anti-SV40 large T antigen (ab16879; Abcam)	1:100
rabbit anti-SV40 large T antigen (#15729; Cell Signaling Technology)	1:200
anti-phospho-Erk1/2 (Thr202/Tyr204) rabbit antibody (#4370; Cell Signaling Technology)	1:100
anti-mouse IgG conjugated to Alexa Fluor 488 goat antibody (A-11029; Thermo Fisher Scientific)	1: 500
anti-rabbit IgG conjugated to Alexa Fluor 546 goat antibody (A-11035; Thermo Fisher Scientific)	1: 500

Antibodies (immunostaining, paraffin section)

Antibody	Antigen retrieval	dilution
rabbit polyclonal antibody against L1CAM (ab123990; Abcam)	microwave (600 W, 10 min) using 10 mM citrate buffer (pH 6.0)	1:100
mouse monoclonal antibody against MT1-MMP (MAB3328; Merck Millipore)	microwave (600 W, 10 min) using 10 mM citrate buffer (pH 6.0)	1:500
rabbit monoclonal antibody against anti-phospho-Erk1/2 (Thr202/Tyr204) (#4370 Cell 1:100Signaling Technology)	microwave (600 W, 10 min) using 10 mM citrate buffer (pH 6.0)	1:100
rabbit polyclonal antibody against APBA3/Mint3 (HPA045577; Sigma)	microwave (600 W, 10 min) using 100 mM Tris-HCl buffer (pH 9.2)	1:100

Supplementary Table 2. Lists of detailed material information.

Factors	n(%)
Average Age (Yr)	58 (28-85)
Primary tumor	
T1b	13 (14.9%)
T1c	41 (47.1%)
T2	30 (34.5%)
T3	1 (1.1%)
T4	2 (2.3%)
Regional lymph nodes	
N0	58 (66.7%)
N1	24 (27.6%)
N2	4 (4.6%)
N3	1 (1.1%)
p-Stage	
IA	42 (48.3%)
IIA	28 (32.2%)
IIB	10 (11.5%)
IIIA	5 (5.7%)
IIIB	1 (1.1%)
IIIC	1 (1.1%)

Supplementary Table 3 Clinicopathological information from 87 patients with invasive breast cancer